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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,512	07/10/2006	Francesco Bellini	50319/006002	6653

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
01/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/577,512	BELLINI ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,18,23 and 25-43* is/are pending in the application.

4a) Of the above claim(s) *14-15, 18, 23, 25-29, 33-34, and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-32,35,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-13, 16-17, 19-22, and 24 have been canceled and claims 14-15, 18, 23, and 25-43 are currently pending.

Election/Restrictions

Applicants' election of group II drawn to a method and the species of sulfonylurea, in the reply filed on 11/19/2008 is acknowledged. The election was made without traverse.

Claims 14-15, 18, 23, 25-29, 33-34, and 36-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group or species, there being no allowable generic or linking claim. Claims 30-32, 35, and 42-43 are under examination in the instant office action.

Priority

The instant application claims priority under 35 U.S.C. § 371 from international application PCT/CA2004/001883, filed October 27, 2004, which claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Application No. 60/514,738, filed October 27, 2003.

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 10/27/2003.

Information Disclosure Statement

A signed and initialed copy of the information disclosure statement filed on 4/27/2006 is enclosed in this action.

Claim objections

Claim 30 is objected because of the following informalities: Claim 30 uses an improper Markush-type language. Applicant is advised to reword "selected from the following types of antidiabetic agents: ……" to "selected from the following types of antidiabetic agents consisting of: ……."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 30-32, 35, and 42-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 5,859,037 (issue date: 6/12/1999) in view of WO 01/15689 (pub date: 3/8/2001, evidenced by its English equivalent, US patent 7,402,611). WO 01/15689 was supplied by Applicant on the IDS received on 4/27/2006.

US patent 5,859,037 teaches a method of treating non-insulin dependent diabetes mellitus (type 2 diabetes) in humans comprising administering to a patient in need of treatment from about 3 mg to about 250 mg of a sulfonylurea antidiabetic agent in combination with about 100 mg to about 1000 mg of a glitazone antidiabetic agent, wherein said amounts are synergistic in the treatment of non-insulin dependent diabetes mellitus (claim 5). It further teaches that glitazone antidiabetic agent is effective for increasing sensitivity of insulin receptor throughout the body, thereby diminishing or eliminating the need for exogenous insulin, (column 1, lines 23-27). Administration of a sulfonylurea in combination with a glitazone encompasses administering two drugs at or about the same time.

The reference differs from the instant claims insofar as it does not specifically teach 4-hydroxyisoleucine including its isomer and further administering insulin.

WO01/15689 teaches 4-hydroxyisoleucine including its isomer, 2S, 3R, 4S isomer of 4-hydroxyisoleucine, which has insulin mimetic and insulin sensitizing effects and is suitable for treating insulin resistance and combating or preventing syndromes linked to insulin resistance, which include type 2 diabetes (p4, lines 15-20 and p11, lines 24-27). It further discloses that the effect of the combination of 4-hydroxyisoleucine and insulin was greater than the effect of insulin or 4-hydroxyisoleucine when used alone (example 4 and figure 5)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the glitazone antidiabetic agent with 4-hydroxyisoleucine including its isomer, 2S, 3R, 4S isomer of 4-hydroxyisoleucine taught by WO01/15689 for the combination with a sulfonylurea in the treatment of type II diabetes as taught by US patent 5,859,037 with a reasonable expectation of success since the glitazone antidiabetic agent and 4-hydroxyisoleucine are functional equivalents as a insulin sensitizer thus reducing insulin resistance as taught by US patent 5,859,037 and WO01/15689. In addition one of ordinary skill in the art at the time the invention was made would have been motivated to further administer insulin since WO01/15689 teaches the synergic effect of 4-hydroxyisoleucine in combination with insulin.

2) Claims 30-32, 35, and 42-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 01/15689 (pub date: 3/8/2001, evidenced by its English equivalent, US patent 7,402,611) in view of DeFronzo (Ann Intern Med., 131:281-303, 1999).

WO 01/15689 teaches 4-hydroxyisoleucine including its isomer, 2S, 3R, 4S isomer of 4-hydroxyisoleucine, which has insulin-mimetic and insulin-sensitizing effects and is suitable for treating insulin resistance and combating or preventing syndromes linked to insulin resistance, which include non-insulin dependent diabetes mellitus (p4, lines 15-20 and p11, lines 24-27; which is evidenced by the DeFronzo reference below). It further discloses that the effect of the combination of 4-hydroxyisoleucine and insulin was greater than the effect of insulin or 4-hydroxyisoleucine when used alone (example 4, and figure 5)

The reference differs from the instant claims insofar as it does not specifically teach the combination of a sulfonylurea antidiabetic agent with 4-hydroxyisoleucine and administering both drugs about or at the same time.

DeFronzo teaches sulfonylureas as oral agent for the treatment of type 2 diabetes (table I and p288, left column, 2nd and 3rd paragraphs). It further teaches that a rational approach to therapy in patients with type 2 diabetes is to begin therapy with a sulfonylurea or metformin and add another oral agent if the desired glycemic control is not achieved, and bedtime insulin or a third agent can be added if additional therapy is required (p300, left column, 3rd paragraph). In addition, it teaches that type 2 diabetes is part of a complex metabolic-cardiovascular cluster of disorders referred to as the insulin resistance syndrome (p289, right column, 2nd paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use 4-hydroxyisoleucine including its isomer, 2S, 3R, 4S isomer of 4-hydroxyisoleucine taught by WO 01/15689 in combination with a sulfonylurea taught by DeFronzo for the treatment of type 2 diabetes with a reasonable expectation of success of getting additive or synergic effects since both drugs are taught to be effective for the treatment of type 2

diabetes by prior art and DeFronzo already teaches the combination of a sulfonylurea with another oral antidiabetic agent and insulin. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine two compositions or treatment each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose…..The idea of combining them flow logically from their having been individually taught in the prior art." See In re Kerkhoven, 626 F. 2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to administering both drug about or at the same time, it would be prima facie obvious to one of ordinary skin in the art at the time the invention was made to try either administering both drugs at the same time or administering them sequentially for the combination therapy based on patients' condition, desired glycemic control, types of formulation, and dose of each drug in order to maximize a synergic effect from both drugs taught to be effective for treating diabetes by prior art.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 30-32, 35, and 42-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-5 of US patent 5,470,879 in view of DeFronzo (Ann Intern Med., 131:281-303, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US patent 5,470,879 are also drawn to using 4-hydroxyisoleucine for the treatment of non-insulin dependent diabetes (type 2 diabetes). The claims of US patent 5,470,879 do not recite the combination of a sulfonylurea antidiabetic agent with 4-hydroxyisoleucine. However, DeFronzo teaches sulfonylureas as an oral agent for the treatment of type 2 diabetes and further teaches that a rational approach to therapy in patients with type 2 diabetes is to begin therapy with a

sulfonylurea or metformin and add another oral agent if the desired glycemic control is not achieved, and bedtime insulin or a third agent can be added if additional therapy is required as stated above in the second 103 rejection. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use 4-hydroxyisoleucine in combination with a sulfonylurea taught by DeFronzo for the treatment of type 2 diabetes with a reasonable expectation of success of getting additive or synergic effects since both drugs are taught to be effective for the treatment of type 2 diabetes by prior art and DeFronzo already teaches the combination of a sulfonylurea with another oral antidiabetic agent and insulin. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine two compositions or treatment each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose…..The idea of combining them flow logically from their having been individually taught in the prior art." See In re Kerkhoven, 626 F. 2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 30-32, 35, and 42-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-9 and 13 of copending application 12/176827 in view of DeFronzo (Ann Intern Med., 131:281-303, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are also drawn to using 4-hydroxyisoleucine for the treatment of insulin resistance and the syndrome associated with insulin resistance which encompasses type 2 diabetes as evidenced by the DeFronzo reference above in the second 103

rejection. The claims of US patent 5,470,879 do not recite the combination of a sulfonylurea antidiabetic agent with 4-hydroxyisoleucine. However, DeFronzo teaches sulfonylureas as an oral agent for type 2 diabetes and further teaches that a rational approach to therapy in patients with type 2 diabetes is to begin therapy with a sulfonylurea or metformin and add another oral agent if the desired glycemic control is not achieved, and bedtime insulin or a third agent can be added if additional therapy is required as stated above in the second 103 rejection. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use 4-hydroxyisoleucine in combination with a sulfonylurea taught by DeFronzo for the treatment of type 2 diabetes with a reasonable expectation of success of getting additive or synergic effects since both drugs are taught to be effective for the treatment of type 2 diabetes by prior art and DeFronzo already teaches the combination of a sulfonylurea with another oral antidiabetic agent and insulin. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine two compositions or treatment each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose…..The idea of combining them flow logically from their having been individually taught in the prior art." See In re Kerkhoven, 626 F. 2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614
Bbs

BONG-SOOK BAEK
Examiner, Art Unit 1614